REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on **April 28, 2008**, and the references cited therewith.

Claims 1-9, 12-13, and 31-33 are now pending in this application. Claims 14-30 and 34-38 have been withdrawn. Claims 5 has been cancelled and claims 3, 6, 7, 9 and 13 have been amended.

Claim 3 has been amended to read "tumor" and not "turnout" cells. Support for this amendment may be found in original claim 3, page 67 of the Specification.

Claims 6 and 7 have been amended to depend on claim 1, rather than claim 5. Support for this amendment may be found in the Specification on page 11, lines 11-15.

Claim 9 has been amended to read "green fluorescent protein" instead of "GFP," and "yellow fluorescent protein" instead of "YFP." Support for this amendment may be found in the Specification on page 11, lines 25-31.

Claim 13 has been amended to replace the term "tenascin" with the term "teneurin". This amendment is to correct a typographical error in the claim. Support for this amendment may be found on page 4, lines 34-35 of the Specification.

Claims 31 and 33 have been amended to direct to a composition which comprises specifically an "intracellular" target rather than any cellular target. Support for this amendment may be found on page 7, lines 27-31 of the Specification

It is believed that no new matter has been added.

Restriction Requirement

On **January 28, 2008**, Applicants provisionally elected, with traverse, to prosecute the invention of Group 1, Claims 1-9, 12-13, and 31-33, but argued that all of the claims are linked by a single general inventive concept, namely detection of teneurin signaling and that there need not be a distinction between detecting signaling by measurement of the cleaved product versus the biological activity of cellular targets thereof (e.g., PML, Zic, ponsin, p53 or myc) because teneurin signaling mechanism of action is the same for the signaling detection. The examiner rejected this argument, arguing that the measurement of the biological activity of cellular targets thereof do not use the same composition as the method of Group I. Without conceding to the

accuracy of the Examiner's argument, Applicants confirm the election, with traverse, to prosecute Group 1, Claims 1-9, 12-13, and 31-33 of the invention.

The claims of the non-elected invention, Claims 10, 11, 14-30 and 36-38 were withdrawn. However, Applicant reserves the right to later file continuations or divisions having claims directed to the non-elected inventions.

Objection

The examiner has objected to claim 3 for a typographical error that appears in the claim and claim 9 for the use of abbreviated language. Applicants have amended claim 3 to correct the typographical error. Applicants have also amended claim 9 to read "green fluorescent protein" instead of "GFP" and "yellow fluorescent protein" instead of "YFP".

Rejection Under Section 112, Second Paragraph

Claim 13 was rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, by providing insufficient antecedent basis for the limitation "said cleaved tenascin" in claim 12.

The Applicants have amended claim 13 to replace the term "tenascin" with the term "teneurin". This amendment is to correct a typographical error in the claim. Support for a method for detecting teneurin signaling wherein the determination of the amount of cleaved teneurin may be found on page 4, lines 34-35 of the Specification. This amendment should obviate the Examiner's rejection for indefiniteness.

In view of the preceding remarks, reconsideration and withdrawal of the objection under Section 112, second paragraph, is respectfully requested.

Rejection Under Section 112, First Paragraph

The Examiner has rejected claims 1-9, 12-13, and 31-33 35 USC 112 first paragraph, as failing to comply with the enablement requirement. The Examiner cited *In re Wands*, 858 F.2d 731 (Fed.Cir. 1988), a case in which the Court of Appeals for the Federal Circuit reversed the Patent Office's finding of nonenablement and identified a variety of factors which may be

relevant to whether practicing a claimed invention would require undue experimentation, including: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The pending claims of the present invention are directed to novel methods for detecting teneurin signaling by measuring the presence of a cleaved teneurin product which comprises a portion of the cytoplasmic domain of teneurin and targets to the cell nucleus. The Examiner admitted that the specification teaches the following: (a) upon cotransfection of N-terminal, cytoplasmic domain of teneurin-1 (the teneurin-1b) and posin, the cytoplasmic domain Teneurin-1b binds to and translocates together with ponsin into the nucleus; (b) antibody to the N-terminus of the trasnfected teneurin-1 fragment, containing the N-terminal transmembrane and cytoplasmic domains of 218 amino acids stains all membrane and as well as the nuclei; (c) the ponsin gene encodes a protein belonging to the Ponsin/ArgBP2/venexin family and that all members of this family contain three SH3 domain which interacts with Vinculin, an F-actin binding protein, at cell-cell and cell-matrix adherens junctions or with Afadin at Zonula adherens; (d) Ponsin also directly interacts with the non-receptor focal adhesion tyrosine kinase p125 FAK; and (e) various scientific references suggest that teneurin-1 could function as receptor protein, transmitting signals to the cell interior upon homo- or heterophillic binding of a ligand or as a membrane bound ligand. The Examiner, however, argued that the specification does not provide data or objective evidence showing that: (i) a signal pathway is induced upon binding of the cleaved cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei; (ii) a signal pathway involved in cell adhesion, cytoskeleton assembly or transcription is induced upon binding of the cleaved cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei; (iii) that cytoplasmic domain of teneurin-1 and ponsin are detected in the nuclei of normal neurons or tumor cells; and (iv) downstream proteins, including those from a pathway influencing cell adhesion, cytoskeleton assembly or transcription, are modulated temporally and spatially in response to the translocation of the cleaved cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei. *Office Action*, p. 4-6. The Examiner therefore found Applicants' statement that "teneurin-1 and ponsin will influence each other's

function in the regulation of cell adhesion, cytoskeleton assembly and possibly transcription" too speculative. The Examiner is essentially challenging the objective truth of the utility of the invention.

Applicants respectfully disagree. The PTO has the initial burden of challenging a presumptively accurate disclosure. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Only after the PTO has provided evidence or reasoning that one skilled in the art would reasonably doubt the enablement provided for in a given invention does the burden then shift to the applicant to rebut the Examiner's contentions. *In re Brandstadter*, 484 F.2d 1395, 1406-07 (CCPA 1973). It is respectfully submitted that the Examiner has not provided any evidence or reasoning within the present Office Action to establish a prima facie case of lack of enablement.

The pending claims of the invention are directed to novel methods for detecting teneurin signaling by measuring the presence of a cleaved teneurin product which comprises a portion of the cytoplasmic domain of teneurin and targets to the cell nucleus. The invention is based on the present inventors' discovery for the first time that "the cytoplasmic domain of teneurin, the cleaved teneurin product of the invention, contains transcriptional activity or acts as a transcriptional modulator." *See Specification*, p. 15. The Specification further discloses that teneurin is involved in intracellular signalling by its cytoplasmic domain interacting with cellular targets that influence gene transcription and are involved in cerebellar development, neuronal differentiation, apoptosis, cell proliferation and senescence. *Id.* at p. 7, lines 18-21.

The specification extensively details experiments evidencing that teneurin, once cleaved, is able to effectuate cellular signaling events via its cytoplasmic domain. Any consideration of teneurin being simply a structural protein is dismissed in the first instance by the evidence presented within the Specification. For instance, Example 1 of the Specification demonstrates that teneurin-2 cytoplasmic domain localizes to the nucleus and co-localizes with PML, which protein is involved in a number of functions associated with transcriptional control. Example 2 of the Specification also shows that teneurin-2 is in fact biologically active and is involved in regulating Zic transcriptional activity. This example extensively details how Zic activity was significantly decreased following the expression of teneurin-2 in transfected cells, suggesting an inhibitory effect of teneurin-2 on the transcriptional activity of Zic. In addition, the

immunoprecipitation experiments of Example 3 of the specification demonstrate that ponsin binds to and co-localizes together with cytoplasmic domain of teneurin-1 into the nucleus. Further, teneurin is not simply active only in its uncleaved state. Through microarray analysis, Example 7 shows that there are a plethora of genes whose expression products are affected either by the presence or absence of the cytoplasmic domain of teneurin. Moreover, the role that these aforementioned genes (e.g., genes listed in Tables 1 and 2) are known to have in the regulation of cell growth, differentiation, and apoptosis, overlaps with the already well-accepted functions of such proteins as PML and ponsin.

The Inventors further demonstrated in Example 4 of the Specification that the morphology of the cells expressing the contructs including the cytoplasmic domains are very different from the ones without the cytoplasmic domain, implying an interaction of teneurin-2 cytoplasmic domain with cytoskeletal components. Similarly, Example 5 shows that clones expressing the longer form of the extracellular domain (TEY) shows a different morphology (flatter morphology) and grow in epithelial cell-like patches compared to the cells expressing the shorter teneurin extracellular domain (TE), suggesting an increase in cell-cell adhesion.

Thus, viewing the examples together, the Specification provides compelling evidence that the cleaved product of teneurin contains transcriptional activity or acts as transcriptional modulator and is translocalized into the nucleus, which undoubtedly affects signal transduction downstream. As such, there would be no reasonable basis for one skilled in the art to doubt that the cleaved cytoplasmic domain of teneurin is able to affect downstream signaling cascades, which play integral roles in the development and lifespan of the cell. The Examiner has not provided any evidence or any reasonable basis as to why binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei would not induce a signal pathway, why its effect on Zic transcriptional regulatory activity would not affect downstream signaling cascade, or why one would not expect the cytoplasmic domain of teneurin-1 and ponsin to be detected in the nuclei of normal neurons or tumor cells in light of the specific examples disclosed in the specification.

The examiner also argued that the specification does not provide any data that specific proteases cleave full length teneurin-1 twice to liberate the cytoplasmic domain. However, it is not necessary that Applicants identify any specific protease or that it cleaves full length teneurin-

1 once or twice. It is important and is sufficient that the full length teneurin is cleaved and liberate the cytoplasmic domain from the membrane, which domain is localized into the nucleus and has transcriptional activities that can affect downstream signal cascade. Is in not completely inconceivable that the full length teneurin is cleaved to liberate transcriptionally active cytoplasmic domain of teneurin, which domain is localized into the cell nucleus to serve some functional purposes.

The Examiner then argued that one cannot predict which cascade of proteins or whether there exist a cascade of proteins at all that are modulated upon binding of the cleaved, cytoplasmic domain of teneurin-1 to ponsin and their translocation into the nuclei. However, the present claims did not mention that the detection of teneurin-1 signaling is through any one distinct signaling cascade or pathway. The claims are simply directed to methods to detect teneurin signaling wherein their essential function, and the scope of which is claimed, is that there exists some type of signaling cascade whereby the cleaved cytoplasmic fragment of teneurin-1 is involved in some type of intracellular signal transduction subsequent to its interaction with proteins such as ponsin. It is not necessary that the precise signaling cascade as put forth in the disclosure be recapitulated in its entirety in order to practice the invention. As well, it is not essential that the Applicants are able to predict which cascade is actually activated by teneurin translocation and protein complex formation with ponsin subsequent to the protein being cleaved.

It is true that in the prior art teneurin, a transmembrane protein, has not been well characterized. Nevertheless, teneurin has been long thought to have some manner of integral involvement in the development of drosophila embryos. *See e.g.*, *Baumgartner et al.* (1994) Embo J 13: 3728-40; *Levine et al.* (1994) Cell 77: 587-98; *Levine et al.* (1997) Dev Dyn 209: 1-14. Teneurin may also play an important role in development not only in drosophila but in vertebrate species as well. *Wang et al.* (1998) Embo. J. 17, 3619-30. Recent studies in chicken have determined that there exists a close correlation between the presence of teneurin and the developing cytoskeleton. As well, there seems to be a correlation with expression of recombinant teneurin-2 in developing chicken embryos and the observation of filopodia formation and enlarged growth cones. *Rubin et al.* (1999) Dev. Biol. 216, 195-209. However, despite the conserved role of teneurin in a number of species (i.e. drosophila, *C. elegans*, and chicken) and

the apparent mode of action whereby in *C. elegans* teneurin-1 becomes cleaved and subsequently translocates to the nucleus, the Examiner contends that one skilled in the art could not predict that this feature, namely cleavage of teneurin, would be present in normal neuron or tumor cells. Essentially, the Examiner's conclusion is on the basis that mouse Ten-m protein splice variants may exist that do not allow for the cleavage of their extracellular domain of teneurin. It is evident that the Examiner has provided adequate support that such variants may exist. However, the Examiner then fails to provide a rationale for why these splice variants would be the only variants of the protein present within the cell. Further, the Examiner does not provide support as to whether such variants would even be predominant in total number in the context of normal neuronal or tumor cells. The Examiner merely concludes that since these variants exist, the predictive force of the invention is then rendered null. However, the Examiner cites no prior art reference or provides any reasonable basis to support the conclusion that the well-established manner of cleaving teneurin-1 would be conserved in some species but not others. As well, it is unclear why the *intracellular* cytoplasmic region of teneurin, in all normal neuronal or tumor cells, would unable to be cleaved in light of the possibility that there may be teneurin-1 variants in mice that resist cleavage of their *extracellular* domain.

Another contention made by the Examiner is that one skilled in the art could not predict that the cytoplasmic domain of teneurin-1 would necessarily form a complex with another target protein aside from ponsin. However, ponsin is not the only protein with which teneurin may form a complex. Rather the cleaved cytoplasmic N-terminal portion of teneurin may actually join with the protein MBD-1 and subsequently translocate to the nucleus. *S.M. Nunes et al.* (2005) Exp. Cell Res. 305 122–132, 131. Moreover, the fact that some experimentation may need to take place to further determine other cellular targets of teneurin-1 does not *a priori* make that experimentation undue. *In re Angstadt,* 190 U.S.P.Q. 214 (C.C.P.A. 1986).

Previously, teneurin had been merely postulated as having a role regarding intracellular signal transduction. The present invention discloses to one skilled in the art that teneurin is in fact involved in cellular signal transduction and that it has a role where it can regulate gene expression via its involvement in transcriptional activity. Peer-reviewed journals and the present data support the notion that the cleaved cytoplasmic fragment of teneurin is stable and has the ability to form a complex with not only ponsin but also other target proteins such as MBD-1.

Therefore, one skilled in the are would not doubt the objective truth of this disclosure. Furthermore, even though one skilled in the art may not necessarily be apprised of the specific signaling pathways that are eventually effected by teneurin-1 signaling via the cleaved cytoplasmic domain of teneurin-1, such experimentation to elucidate these pathways is not necessarily given that claims are directed to a method to detect teneurin signaling (i.e., an assay) and significant guidance and exemplification has been given as to how to practice the methods of the invention. Even though the Examiner stated that one skilled in the art would need undue experimentation to practice the claimed invention, it is unclear why one skilled in the art is required to predict a signal pathway or identify which specific signal pathway is induced by binding of the cytoplasmic domain of teneurin to ponsin in order to practice the claimed invention.

In summary, Applicants emphasize that the claimed invention is essentially directed at an assay. The totality of the data presented in the specification provides compelling circumstantial evidence that teneurin-1 effects downstream cytokine signaling once the protein has been cleaved and has then translocated to the nucleus of the cell. The claims are not overly broad given what has already been determined: that it is highly likely and predictable that the cleaved cytoplasmic domain of teneurin-1 and its fragments, which has transcriptional activities, will affect downstream signal transduction, and that the aforementioned domain is also capable of forming complexes with other target proteins aside from ponsin. For reasons stated above, it is respectfully submitted that the Examiner's analysis and subsequent rejection of the present claims failed establish a prima facie case of lack of enablement. Therefore, withdrawal of the rejection for lack of enablement is respectfully requested.

Rejection under Section 102

Claim 31 was rejected under 35 USC 102(b) as anticipated by Minet et al, 1999, J. Cell Science, 112: 2019-2032.

As a preliminary matter, Applicants note that the Examiner's argument regarding the claim being anticipated by the prior art is rendered moot in view of the current amendment to claims 31 and 33 to refer unambiguously to an "intracellular target". Nonetheless, Applicants believe that the original basis for rejection was not correct for the following reasons.

The Examiner contends that Minet et al teach of a "C-terminal fragment of teneurin-1, containing [a] YD repeat, [and] binds to heparin sulfate in cell extracts." While this is correct, the fragment that Minet teaches is actually extracellular. This is in stark contrast to the fragment that is disclosed within the present application, which is intracellular. Example 2 of the present application discloses of a teneurin-2 fragment whose "cytoplasmic domain" translocates to the nucleus. As well, Example 6 discloses that the extracellular portion of teneurin-2 undergoes homophilic binding whereby the intracellular, "cytoplasmic domain," of the protein is subsequently cleaved but remains stable. Similarly, Example 9 details how antibodies were raised against the N-terminus of teneurin-1 to detect the protein's presence within the nucleus of embryonic *C.elegans* cells. Moreover, the present application discloses that the cleaved teneurin fragment translocates to the nucleus. Minet et al simply teaches that the extracellular teneurin fragment that they have discovered has a C-terminus region that binds to heparin and that subsequent to this binding action that the protein is released "from high molecular mass aggregates." *Minet et al.*, (1999) J. Cell Sci. 112, 2019-32 (abstract).

The Examiner's single prior art reference can only anticipate the present invention if that prior art reference teaches "each and every element" as described within the given claims for the present invention. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987). The present application discloses and now claims an intracellular, cytoplasmic fragment that undergoes a cleaving process. This is in contrast to the extracellular teneurin fragment disclosed by Minet et al that is released to an undisclosed location upon the binding of heparin to repetitive sequence motifs located on the proteins C-terminus.

In view of the preceding remarks, reconsideration and withdrawal of the objection under Section 102, is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone the below-identified attorney to facilitate prosecution of this application.

This response is filed within the shortened statutory period of three months from the date of the mailing of the non-final office action, and therefore, it is believed no fees are due. Should

this be incorrect, the Commissioner is authorized to charge any additional fees, or credit any overpayment, to deposit account No. 50-4255.

Respectfully submitted,

Date 7/23/2008

By _____
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